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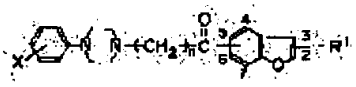
(54) BENZOFURAN DERIVATIVE AND MEDICINAL COMPOSITION CONTAINING THE SAME

(57)Abstract:
PURPOSE: To obtain a new benzofuran derivative having ω-(4-phenylpiperadinyl) acyl side chain on the benzene ring side, useful as a medicine capable of improving a ratio causing cardiac infarction or unexpected death, especially an antihypertensive agent.
CONSTITUTION: This benzofuran derivative is represented by formula I [R1 is H, a halogen, an alkyl or an N'-1-6C alkylcarbohydrazonomethyl; X is H, a halogen, a 1-6C alkyl or a 1-6C alkoxy; (n) is 0-10], e.g. 5-[4-(2-methoxyphenyl) piperazinylcarbonyl]benzofuran. The compound of formula I, e.g. the compound of formula I in which (n) is 0 is obtained by reacting a bromophenol of formula II with a bromoacetoaldehydediethylacetal of formula III under alkaline conditions, cyclizing the resultant compound to afford bromobenzofuran of formula IV, changing bromo group to cyano group to provide cyanobenzofuran, hydrolyzing the compound to afford a carboxylic acid of formula V and finally condensing the carboxylic acid of formula V with N-phenylpiperazine.

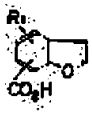


I

II

III

IV



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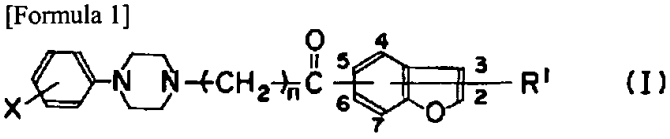
LEGAL STATUS

CLAIMS

[Claim(s)]
[Claim 1] The benzofuran derivative shown by the general formula (I), and its salt permitted pharmacologically.
[Formula 1]



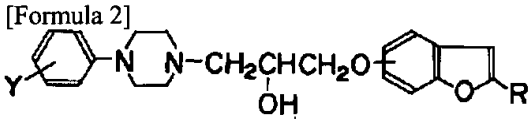
(I)

(R1 expresses a hydrogen atom, a halogen atom, the alkyl group of C1-C6, or N'-C1 - C6 alkyl KARUBO hydrazono methyl group among a formula, and X expresses a hydrogen atom, a halogen atom, the alkyl group of C1-C6, or the alkoxy group of C1-C6, and n expresses the integer of 0-10.)
[Claim 2] The compound according to claim 1 which R1 replaces by 4- of a benzofuran ring, 5-, 6-, or 7-grades, and is characterized by expressing a hydrogen atom, a halogen atom, or the alkyl group of C1-C6.
[Claim 3] R1 replaces by 2- of a benzofuran ring, or 3-grades, and it is N'. - Compound according to claim 1 characterized by expressing C1 - C6 alkyl KARUBO hydrazono methyl group.
[Claim 4] The compound according to claim 3 characterized by R1 having replaced by 2-grades of a benzofuran ring.
[Claim 5] A compound given in any 1 term of the claims 1-4 characterized by n expressing the integer of 0-2.
[Claim 6] A compound given in any 1 term of the claims 1-4 characterized by n being 0 or 2.
[Claim 7] The physic constituent which contains the benzofuran derivative shown by the general formula (I) according to claim 1, or its salt permitted pharmacologically as an active principle.
[Claim 8] The physic constituent of a claim 7 with which a physic constituent is used as a lipid fall nature antihypertensive.

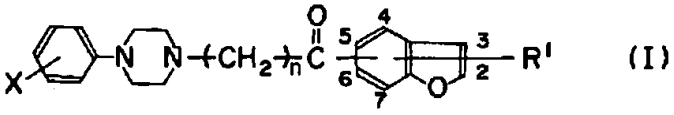
[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] a benzofuran derivative with a new this invention, and the physic constituent containing it -- it is related with a lipid fall nature antihypertensive in detail
[0002]
[Description of the Prior Art] Development of the physic for circulatory organs which makes a benzofuran derivative an active principle is performed variously conventionally. Also in it, there are some reports about the benzofuran derivative system antihypertensive (hypotensor) which has 4-phenyl piperazinyl machine.
[0003] For example, the benzofuran derivative shown by the general formula of the following-izing 2 as an antihypertensive which has alpha-interception operation and calcium antagonism is indicated by JP,60-202872,A and JP,61-218582,A.
[0004]
[Formula 2]

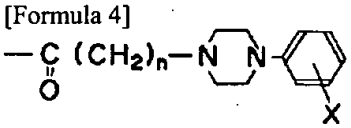


[0005] (R expresses an acetyl group, a carbamoyl group, a cyano group, a low-grade alkoxy carbonyl group, a carboxyl group, or 1-hydroxyethyl machine among a formula, and Y expresses a hydrogen atom, a lower alkoxy group, a low-grade alkyl group, or a halogen atom.)
Moreover, the benzofuran derivative which contains also in JP,64-70480,A the dog non derivative which has 4-phenyl piperazinyl machine is indicated as an antihypertensive which has calcium antagonism.
[0006] Although high blood pressure is the important risk factor of the circulatory system illness, it is comparatively easy by development of present, for example, the above various antihypertensives, to lower the blood pressure of the hypertensive. However, even if it prescribes an antihypertensive for the patient, the present condition is that the rate which results in myocardial infarction or sudden death seldom improves.
[0007] Therefore, it waited for development of the antihypertensive which can improve these rates. As a compound similar to this invention compound on the other hand As matter which has central action, for example, Indian J.Chem., Sect.B, 28B (5), Although some compounds which have omega-(4-phenyl piperazinyl) acyl side chain in 385 (1989) or Acta.Pol.Pharm., 44 (6), and 497 (1987) at 2- [of a benzofuran ring] or 3-grade, i.e., furan ring, side are known The compound which has omega-(4-phenyl piperazinyl) acyl side chain in 4-, 5-, 6-, or 7-grade, i.e., the benzene ring, side is not known.
[0008]
[Problem(s) to be Solved by the Invention] this invention is made from the above-mentioned viewpoint, and makes it a technical problem effectively to offer the physic which can improve the rate which results in myocardial infarction or sudden death, and the new benzofuran derivative which can be used and which has omega-(4-phenyl piperazinyl) acyl side chain in a benzene ring side especially as an antihypertensive.
[0009]
[Means for Solving the Problem] This invention persons note that the antihypertensive having hypolipidemic action needs to be developed to improve the rate which results in myocardial infarction or sudden death. The result which repeated improvement research about the benzofuran derivative conventionally known as an antihypertensive, The new benzofuran derivative which has omega-(4-phenyl piperazinyl) acyl side chain in the benzene ring side of a benzofuran ring, i.e., 4-, 5-, 6-, or 7-grades It found out having the hypolipidemic action which was not seen at all in the benzofuran derivative system antihypertensive which has omega-(4-phenyl piperazinyl) acyl side chain in the furan ring side, i.e., 2- or 3-grades, of the former, for example, a benzofuran ring, and this invention was completed.
[0010] That is, this invention offers the benzofuran derivative shown by the following general formula (I), and its salt permitted pharmacologically.
[0011]
[Formula 3]

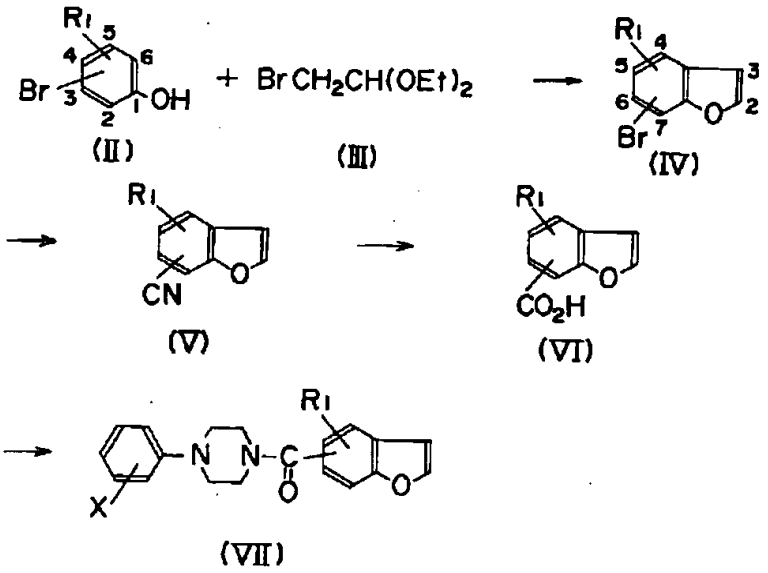


(I)

[0012] (R1 expresses a hydrogen atom, a halogen atom, the alkyl group of C1-C6, or N'-C1 - C6 alkyl KARUBO hydrazono methyl group among a formula, and X expresses a hydrogen atom, a halogen atom, the alkyl group of C1-C6, or the alkoxy group of C1-C6, and n expresses the integer of 0-10.)
this invention offers the physic constituent especially useful as a lipid fall nature antihypertensive which contains the benzofuran derivative shown by the aforementioned general formula (I), or its salt permitted pharmacologically as an active principle again.
[0013] Hereafter, this invention is explained in detail. Although the benzofuran derivative of this invention is a compound shown by the above-mentioned general formula (I), the details, such as a basis which substituent R1;X of a general formula (I) combines, are as follows.
[0014] <Substituent R1> R1 is a hydrogen atom, a halogen atom, or N' especially, although a hydrogen atom, a halogen atom, the alkyl group of C1-C6, or N'-C1 - C6 alkyl KARUBO hydrazono methyl group is expressed. - C1 - C6 alkyl KARUBO hydrazono methyl group is desirable.
[0015] In addition, when R1 is a hydrogen atom, a halogen atom, or the alkyl group of C1-C6, it is desirable to have replaced by the benzene ring side of a benzofuran ring, i.e., 4- of a benzofuran ring, 5-, 6-, or 7-grades. Moreover, R1 is shown by N'-C1-C6 alkyl KARUBO hydrazono methyl group [-CH=NNHCOR2 (R2 is the alkyl group of C1-C6).] It is desirable to have come out and to have replaced by the furan ring side of a benzofuran ring, i.e., 2- of a benzofuran ring or 3-grades, in a certain case, and having replaced by 2-grades of a benzofuran ring is more more desirable still.
[0016] Although any of a chlorine atom, a bromine atom, or a fluorine atom are sufficient as a halogen atom when R1 is a halogen atom, a chlorine atom is desirable especially. When R1 is the alkyl group of C1-C6, as this alkyl group, a methyl group, an ethyl group, n-propyl group, i-propyl group, n-butyl, a sec-butyl, a tert-butyl, n-pentyl machine, n-hexyl machine, etc. are mentioned.
[0017] R1 is N'. - When it is C1 - C6 alkyl KARUBO hydrazono methyl group, as this alkyl group of C1-C6, a methyl group, an ethyl group, n-propyl group, i-propyl group, n-butyl, a sec-butyl, a tert-butyl, n-pentyl machine, n-hexyl machine, etc. are mentioned like the case of R1.
[0018] About the < substituent X, although any of a chlorine atom, a bromine atom, or a fluorine atom are sufficient as a halogen atom when >X is a halogen atom, a chlorine atom is desirable especially.
[0019] When X is the alkyl group of C1-C6, as this alkyl group, a methyl group, an ethyl group, n-propyl group, i-propyl group, n-butyl, a sec-butyl, a tert-butyl, n-pentyl machine, n-hexyl machine, etc. are mentioned.
[0020] When X is the alkoxy group of C1-C6, as this C1 - C6 alkoxy group, a methoxy machine, an ethoxy basis, n-propoxy group, i-propoxy group, an n-butoxy machine, a sec-butoxy machine, a tert-butoxy machine, n-pentoxy machine, n-HEKISOKISHI machine, etc. are mentioned.
[0021] Moreover, although X may be replaced by any of o-, m-, or p-grade to a piperazinyl machine, having replaced by o-grade especially is desirable. although n is the integer of 0-10 -- desirable -- 0, 1, or 2 -- it is 0 or 2 still more preferably
[0022] In addition, although the substituent which X combines, i.e., the piperazinyl carbonyl group of the following-izing 4, may be replaced by which position of 4- of a benzofuran ring, 5-, 6-, or 7-grades, it is desirable to have replaced by 5-grades or 7-grades especially.
[0023]
[Formula 4]

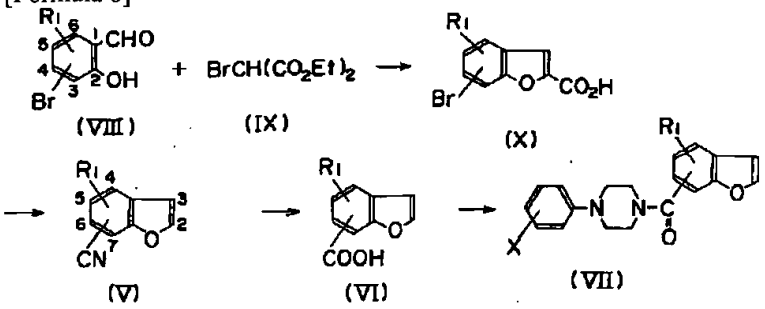


[0024] In this invention, the salt of the benzofuran derivative shown by the general formula (I) is a salt of the mineral acid which can be permitted as physic, or an organic acid, for example, a hydrochloride, a sulfate, a nitrate, acetate, an oxalate, a tartrate, a citric acid salt, a lactate, etc. are mentioned.
[0025] The benzofuran derivative shown by the general formula (I) of this invention can be manufactured, for example by the following method A-D. In addition, although especially the amount of the reaction agent used which participates in a reaction directly is not explained to an all directions method, all are the amounts of stoichiometries.
[0026] The <manufacture method (1) of compound of general formula (I)> method A : as this method is shown in the following-ization 5 A BUROMO phenol (II) and a BUROMO acetaldehyde diethyl acetal (III) are made to react under alkali conditions. Cyclize this reactant and consider as a bromobenzo furan (IV), and change the BUROMO machine of this bromobenzo furan into a cyano group, and it considers as a cyano benzofuran (V). Subsequently, it is the method of understanding this an added water part, considering as a carboxylic acid (VI), making this carboxylic acid condensing with N-phenyl piperazine finally, and obtaining the purpose compound (VII).
[0027]
[Formula 5]

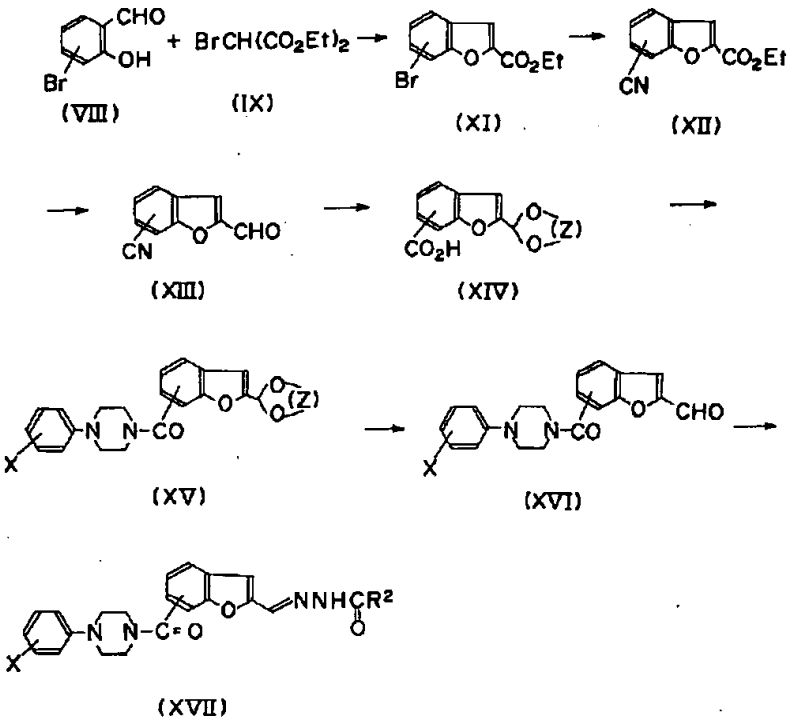


[0028] (R1 expresses a hydrogen atom, a halogen atom, or the alkyl group of C1-C6 among a formula, and X expresses a hydrogen atom, a halogen atom, the alkyl group of C1-C6, or the alkoxy group of C1-C6.)
By this method, a bromobenzo furan (IV) is first manufactured through the following two stages.
[0029] On a first-stage story, a BUROMO phenol (II) is made to react with a BUROMO acetaldehyde diethyl acetal (III), and is acetalized. This reaction is usually performed to the bottom of existence of a base among an organic solvent. As a base used here, a sodium hydroxide, a potassium hydroxide, carbonic acid NTORIUMU, potassium carbonate, a sodium hydride, a triethylamine, etc. are mentioned, for example. Moreover, as an organic solvent, an acetonitrile, a tetrahydrofuran, a dioxane, N.N-dimethylformamide, dimethyl sulfoxide, an acetone, a methyl ethyl ketone, ethanol, etc. are mentioned, for example.
[0030] What is necessary is not to restrict especially the reaction temperature and reaction time of a first-stage story, but just to make them usually react at the arbitrary temperature from ice-cooling to reflux for 15 minutes to about 24 hours. After this resultant performs extraction by the usual processing means, for example, a solvent, separation by the chromatography, crystallization, distillation, etc. and isolates or refines them, it is used for the next reaction. In addition, especially the resultant obtained in the following processes or stages although not indicated shall be isolated or refined with the same processing means (the same is said of method B-D).
[0031] In the second phase, the obtained resultant (acetal) is cyclized under existence of an acid catalyst by suitable organic-solvent Naka or suitable neatness. As an organic solvent, benzene, toluene, a xylene, etc. are usually used.
[0032] What is necessary is not to restrict especially the reaction temperature and reaction time of the second phase, but just to make them usually react at the arbitrary temperature from ice-cooling to 300 degrees C for 15 minutes to about 24 hours.
Next, a cyano benzofuran (V) makes this bromobenzo furan (IV) and a metal cyanide compound react by suitable organic-solvent Naka or suitable neatness, and is obtained. As a metal cyanide compound, although a potassium cyanide, a sodium cyanide, a copper cyanide, etc. are mentioned, for example, a copper cyanide is desirable especially here. As an organic solvent, a pyridine, a quinoline, N.N-dimethylformamide, N-methyl pyrrolidone, hexamethylphosphoramide (HMPA), etc. can be used, for example.
[0033] What is necessary is not to restrict especially the reaction temperature and reaction time in this process, but just to make them usually react at the arbitrary temperature from ice-cooling to 300 degrees C for 15 minutes to about 24 hours.
Next, a carboxylic acid (VI) understands this cyano benzofuran (V) an added water part with an acid or alkali, and is obtained. As an acid used here, a hydrochloric acid, a hydrobromic acid, a sulfuric acid, a nitric acid, an acetic acid, formic acid, etc. are mentioned, and a sodium hydroxide, a potassium hydroxide, a barium hydroxide, etc. are mentioned as alkali, for example. Such acids or alkali are used dissolving in solvents, such as water, lower alcohols (a methanol, ethanol, an isopropanol, propanol, etc.), a dioxane, a tetrahydrofuran, organic acids (however, the case of acidolysis, for example, a carboxylic acid, a sulfonic acid, etc.), and those mixture.
[0034] What is necessary is not to restrict especially the reaction temperature and reaction time in this process, but just to make them usually react at the arbitrary temperature from ice-cooling to reflux for 15 minutes to about 24 hours. 4-phenyl piperazinyl carbonyl benzofuran (VII) which is the last purpose compound makes this carboxylic acid (VI) and N-phenyl piperazine condense, and is obtained.
[0035] This condensation reaction is performed by making it react with an amine or carrying out dehydration to a direct amine, once it leads a carboxylic acid (VI) to carboxylic-acid derivatives, such as an acid chloride, an acid anhydride, ester, and an amide.
[0036] Method B : (2) Make a BUROMO salichlaldehyde (VIII) and diethyl BUROMO malonate (IX) react under alkali conditions, as this method is shown in the following-ization 6. Subsequently, after understanding an added water part and obtaining a bromobenzo furancarboxylic acid (X), the BUROMO machine of this carboxylic acid is changed into a cyano group, and a decarboxylation is carried out further, and it considers as a cyano compound (XI), next, is the same method as

the final process of Method A about this, and is the method of obtaining the same purpose compound (VII) as Method A.
[0037]
[Formula 6]

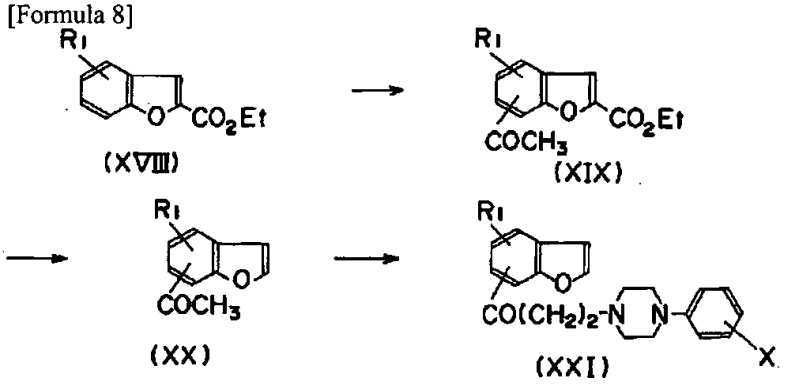


[0038] (R1 expresses a hydrogen atom, a halogen atom, or the alkyl group of C1-C6 among a formula, and X expresses a hydrogen atom, a halogen atom, the alkyl group of C1-C6, or the alkoxy group of C1-C6.)
By this method, first, after making a BUROMO salichlaldehyde (VIII) and diethyl BUROMO malonate (IX) usually react to the bottom of existence of a base among an organic solvent, a carboxylic acid (X) understands this reactant (carboxylate) an added water part, and is obtained. the base used here, an organic solvent, and the first-stage story (reaction of a BUROMO phenol and BUROMO acetaldehyde diethylether) of the first process [in / Method A / in a reaction condition] (manufacturing process of a bromobenzo furan (IV)) -- being the same .
[0039] Next, this carboxylate is understood an added water part with an acid or alkali, and it considers as a carboxylic acid (X). The acid used by this adding-water decomposition reaction or alkali, a solvent, and a reaction condition are the same as that of the case of the adding-water decomposition reaction of the aforementioned method A, and are good.
[0040] Next, a cyano benzofuran (V) can manufacture this bromobenzo furancarboxylic acid (X) by the same method as the conversion reaction from a BUROMO object (IV) to the cyano object (V) of the aforementioned method A. However, at the conversion reaction in the case of Method B, decarboxylation occurs simultaneously and the target cyano object (V) is acquired. The metal cyano compound used at the conversion reaction of Method B, an organic solvent, and a reaction condition are the same as that of the case of Method A, and are good.
[0041] The process of after that until it obtains the last purpose compound (VII) is performed by the same method as the manufacturing process of the benzofuran carboxylic acid (VI) by the adding-water decomposition reaction of the cyano benzofuran (V) of Method A, and the manufacturing process of 4-phenyl piperazinyl carbonyl benzofuran (VII) by the condensation reaction of this carboxylic acid (VI) and N-phenyl piperazine.
[0042] Method C : (3) Make a BUROMO salichlaldehyde (VIII) and diethyl BUROMO malonate (IX) react under alkali conditions, as this method is shown in the following-ization 7. Change the BUROMO machine of the obtained benzofuran-2-carboxylic-acid ethyl (XI) into a cyano group, and it considers as a cyano compound (XII). The carboxylate of 2-grades of this compound is guided to 2-aldehyde object (XIII). Subsequently, after acetalizing by ethylene glycol etc. and considering as an acetal object (XIV) Understand a cyano group an added water part and consider as a carboxylic acid (XIV), and amidate this by N-phenyl piperazine and it considers as an amide object (XV). Subsequently, after understanding the acetal machine of this amide object an added water part and considering as an aldehyde object (XVI), it is the method of obtaining the hydrazide (XVII) of the purpose compound with a suitable hydrazine compound.
[0043]
[Formula 7]



[0044] (R2 expresses the alkyl group of C1-C6 among a formula, and X expresses a hydrogen atom, a halogen atom, the alkyl group of C1-C6, or the alkoxy group of C1-C6, and Z expresses the ethylene or the propylene chain which may be replaced respectively.)
Cyclization and hydrolysis of the first process can be performed by this method by the same method as the first process (manufacturing process of a bromobenzo furancarboxylic acid (X)) of Method B. Moreover, cyano-ization of the second process can be performed by the same method as the conversion process to the cyano group of the BUROMO machine stated by Methods A and B.
[0045] In this way, obtained 2-carboxylate (XII) can be guided to 2-aldehyde object (XIII) by the following usual methods. for example, -- after returning to a metal alkoxide by the ** metal hydride, or it understands ester (XII) an added water part and makes it into a direct aldehyde (XIII) -- ** -- once returning to alcohol by the metal hydride, after oxidizing to an aldehyde (XIII) or understanding an added water part to a ** carboxylic acid, it can return to alcohol by the metal hydride, and can oxidize to an aldehyde (XIII) further As a metal hydride used here, a lithium aluminum hydride, hydrogenation aluminum sodium, a trimethoxy lithium aluminum hydride, a TORIETOKISHI lithium aluminum hydride, hydrogenation aluminum, etc. are mentioned, for example. These metal hydrides can be used in an organic solvent like tetrahydrofurane. In addition, it is desirable to use a lithium aluminum hydride in tetrahydrofurane by the method of returning a carboxylic acid to alcohol like the method of **. Moreover, after guiding a carboxylic acid to a mixed acid anhydride by the method of going via a carboxylic acid like the method of **, it may be advantageous if it returns to alcohol.
[0046] Moreover, hydrolysis can be performed by the same method as the hydrolysis process of the carboxylate in Method B. Moreover, as an oxidizer used at an oxidization process, manganese dioxide, a chromic acid, organic peroxide, DMSO (dimethyl sulfoxide), etc. are mentioned, for example.
[0047] The fourth following process is a process which understands a cyano group an added water part, after guiding and protecting the aldehyde group of 2-aldehyde object (XIII) acquired in this way to an annular acetal (XIV).
[0048] The first-stage story which acetalizes an aldehyde group is usually performed to the bottom of existence of an acid catalyst and a diol among an organic solvent. As an acid catalyst used here, p-toluenesulfonic acid, a hydrochloric acid, a sulfuric acid, formic acid, an acetic acid, a cation exchange resin, etc. are mentioned, for example. As a diol, glycerol, 1, 3-propanediol, 2, and 2-JI etc. is mentioned, for example. Moreover, as an organic solvent, benzene, toluene, a xylene, a tetrahydrofuran, a dioxane, an acetonitrile, chloroform, etc. are mentioned, for example.
[0049] What is necessary is not to restrict especially the reaction temperature and reaction time of this first-stage story (acetalization), but just to make them usually react at the arbitrary temperature from ice-cooling to reflux for 15 minutes to about 24 hours. The second phase which understands the following acetal an added water part is usually performed under existence of an acid catalyst among a solvent. As an acid catalyst used here, a hydrochloric acid, a sulfuric acid, a nitric acid, perchloric acid, an acetic acid, formic acid, oxalic acid, etc. are mentioned, for example. Moreover, as a solvent, water, a methanol, ethanol, an isopropanol, propanol, a dioxane, a tetrahydrofuran, etc. can be used, for example.
[0050] The fifth process is a process which understands the acetal of an amide (XV) an added water part, and is returned to an aldehyde (XVI). This process is performed by the same method as hydrolysis of the second phase of a front process.
[0051] The last process is a process which alkylation acylhydrazine is made to react to an aldehyde (XVI) in an organic solvent, and obtains acylhydrazine (XVII). As an organic solvent used here, an acetic acid, a methanol, ethanol,

N.N-dimethylformamide, a pyridine, etc. are mentioned, for example.
[0052] What is necessary is not to restrict especially the reaction temperature and reaction time in this process, but just to make them usually react at the arbitrary temperature from ice-cooling to reflux for 15 minutes to about 24 hours.
[0053] Method D : (4) As shown in the following-ization 8, use this method as the acyl object (XIX) which acylates 2-ethoxycarbonyl benzofuran derivative (XVIII) and corresponds. After hydrolyzing the ester of 2-grades of this acyl object, carry out a decarboxylation and it considers as an acyl object (XX). It is the method of making the last carrying out the Mannich reaction of this acyl object (XX) to N-phenyl piperazine and formaldehyde (or paraformaldehyde), and manufacturing the purpose compound (XXI).
[0054]
[Formula 8]



[0055] (R1 expresses a hydrogen atom, a halogen atom, or the alkyl group of C1-C6 among a formula, and X expresses a hydrogen atom, a halogen atom, the alkyl group of C1-C6, or the alkoxy group of C1-C6.)
By this method, acylation of the first process is usually performed under existence of an acid catalyst among an organic solvent by the Friedel Crafts reaction with 2-ethoxycarbonyl benzofuran derivative (XVIII), an acid chloride, or an acid anhydride. As an acid catalyst used here, an aluminum chloride, ferric chloride, a titanium trichloride, chlorination tin, a zinc chloride, hydrogen fluoride, a sulfuric acid, a polyphosphoric acid, etc. are mentioned, for example. As an organic solvent, nitrobenzene, carbon-disulfide, dichloromethane, carbon-tetrachloride, 1, and 2-dichloroethane etc. is mentioned, for example.
[0056] What is necessary is not to restrict especially the reaction temperature and reaction time of the first process, but just to make them usually react at the arbitrary temperature from ice-cooling to reflux for 15 minutes to about 24 hours. Next, the carboxylate of the acyl object (XIX) acquired in this way is taken as the acyl object (XX) which carries out a decarboxylation and corresponds, after hydrolyzing. Hydrolysis of this process can be performed by the same method as the hydrolysis process (process which understands a cyano benzofuran (V) an added water part, and manufactures a benzofuran carboxylic acid (VI)) of Method A. Then, the decarboxylation of the obtained carboxylic acid is usually carried out under existence of a copper catalyst among an organic solvent. As an organic solvent used here, N.N-dimethylformamide, a quinoline, etc. are mentioned, for example. The reaction temperature of a decarboxylation stage has a desirable elevated temperature exceeding ordinary temperature, and especially its heating reflux temperature is desirable. Although especially the reaction time in this case is not restricted, it is usually 15 minutes - about 24 hours.
[0057] Finally, this acyl object (XX) is made to usually react with N-phenyl piperazine, formaldehyde, or a paraformaldehyde under Mannich-reaction conditions and in a solvent, and the purpose compound (XXI) is manufactured. As a solvent used here, water, a methanol, ethanol, n-propanol, n-butanol, a dioxane, etc. are mentioned, for example. What is necessary is not to restrict especially the reaction temperature and reaction time of this Mannich reaction, but just to make them usually react at the arbitrary temperature from ice-cooling to reflux for 15 minutes to about 24 hours.
[0058] It is a new compound, and each benzofuran derivative of this invention manufactured as mentioned above has a lipid fall operation with the anti-high-blood-pressure operation which was excellent with the medicinal action mentioned later, therefore is useful as a new lipid fall nature antihypertensive.
[0059] In case the compound of this invention is used as medicine, this compound can be considered as the tablet according to the medication method with the usual tablet support. For example, in internal use, forms, such as a tablet, a capsule, a granule, powder, and liquid medicine, prepare a medicine. In case the solid tablet for internal use is prepared, the excipient of common use, a binder, a lubricant, a coloring agent, disintegrator, etc. can be used. As an excipient, a lactose, starch, talc, a magnesium stearate, a crystalline cellulose, a methyl cellulose, a carboxymethyl cellulose (CMC), a glycerol, a sodium alginate, gum arabic, etc. are mentioned, for example. As a binder, there are polyvinyl alcohol (PVA), a polyvinyl ether, an ethyl cellulose, gum arabic, a shellac, sucrose, etc., for example. As a lubricant, a magnesium stearate, talc, etc. are mentioned, for example. As a coloring agent, there is a Tartrazine aluminium lake (Tartrazine) etc., for example. Moreover, hydroxypropylcellulose, a carboxymethyl cellulose, and starches are mentioned as disintegrator. In addition, when using it as a tablet, being immersed, a spray, an application, etc. may coat the compound of this invention with the well-known method. Moreover, liquefied tablets may be water or oily suspension, a solution, syrup, an elixir agent, etc., and are prepared according to a conventional method. In the case of an injection agent, pH regulator, a buffer, a stabilizing agent, an isotonic agent, a local anesthetic, etc. can be added to this invention compound, and it can prepare the injection agent for the inside of

a vein in hypodermically and muscles according to a conventional method. In the case of a suppository, fats and oils, such as cacao butter, a polyethylene glycol, lanolin, fatty-acid triglyceride, and Witepsol (dynamite Nobel's registered trademark), can be used as a basis.
[0060] In this way, although the amount of medication of the tablet prepared changes with a patient's symptom, weight, age, etc. and it is not generally decided, the amount from which this invention compound usually becomes the range of about 10-2000mg per day by adult's case is desirable. Moreover, it is desirable to usually prescribe a medicine for the patient in 1 - 4 steps per day in this case.
[0061]
[Example] An example explains in more detail the lipid fall nature antihypertensive which contains in below the manufacture method of the benzofuran derivative of the general formula (I) which is this invention compound, and this compound.
[0062]
[Example 1] Manufacture of 5-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran (compound 1). [0063] (1) The solution which dissolved manufacture 5-BUROMO phenol 35.0g of 5-bromobenzo furan and BUROMO diethyl acetal 40.0g in 100ml of N.N-dimethylformamide was carried out under ** under ice-cooling into the suspension of 100ml of N.N-dimethylformamide of 8.9g of sodium hydrides. After carrying out the heating reflux of the obtained reaction mixture for 6 hours, it cooled to the room temperature and water was added. Ethyl acetate extracted the water layer, the organic layer was rinsed, and it dried with magnesium sulfate. Reduced pressure distilling off of the solvent was carried out, 45g [of polyphosphoric acids] and benzene 500ml was added to the obtained residue, and heating reflux was carried out for 2 hours. After cooling the obtained reaction mixture to a room temperature, the supernatant liquid was decanted and taken, the residue was washed by n-hexane, and reduced pressure distilling off was carried out together with the supernatant liquid. The silica gel column chromatography which makes n-hexane an eluate refined the residue, and 5-bromobenzo furan 28.0g (70% of yield) was obtained as oily matter.
[0064] NMR delta (CDCl3):6.72 (1H, dd), 7.24 (1H, dd), 7.42 (1H, d), 7.57 (1H, d), 7.63 (1H, d)
[0065] (2) The solution which dissolved 5-bromobenzo furan 18.0g and 9.6g of copper cyanides obtained with the manufacture above (1) of 5-cyano benzofuran in 50ml of N.N-dimethylformamide was flowed back for 6 hours. After cooling the obtained reaction mixture to a room temperature, the solid-state which added water and deposited was separated and rinsed. 30ml [of water] and ethylenediamine 18ml was added to this solid-state, chloroform extracted the water layer 3 times, and it dried with magnesium sulfate. Reduced pressure distilling off of the solvent was carried out, and the silica gel column chromatography which makes an eluate an n-hexane - ethyl-acetate mixed solvent (it is 10:1 at a capacity factor) refined the obtained residue. Subsequently, vacuum concentration of the fraction containing the specified substance was carried out, and 5-cyano benzofuran 9.1g (72% of yield) was obtained as a crystal which deposits.
[0066] Melting point: 87-88-degree-CNMR delta (CDCl3) : 6.72-6.73 (1H, dd), 7.26 (2H, S), 7.42 (1H, dd), 7.96 (1H, d)
[0067] (3) Ethylene glycol 100ml and 100ml of water were added to potassium hydroxides [which were obtained with the manufacture above (2) of 5-benzofuran carboxylic acid / 5-cyano benzofuran 13.0g and 12.0g of potassium hydroxides] mixture, and heating reflux was carried out for 2 hours. After cooling the obtained reaction mixture to a room temperature, it was made acid by the concentrated hydrochloric acid, ethyl acetate extracted the water layer, saturation brine washed the organic layer, and it dried with magnesium sulfate. Vacuum concentration of the solvent was carried out and 13.5g (91% of yield) of crystals of 5-benzofuran carboxylic acid was obtained.
[0068] Melting point: 168-172-degree-CNMR delta (CDCl3) : 6.88 (1H, d), 7.57 (1H, d), 7.71 (1H, d), 8.10 (1H, d), 8.45 (1H, d)
[0069] (4) 0.1ml [of N.N-dimethylformamide] and thionyl chloride 1.8g was added to the suspension which made 1 and 2-dichloroethane 10ml suspend 2.0g of 5-benzofuran carboxylic acids obtained with the manufacture above (3) of 5-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran, and heating reflux was carried out for 1 hour. After carrying out reduced pressure distilling off of the solvent, the dichloromethane was added to the residue and it considered as the solution, and this solution was used as the solution which dissolved 1-(2-methoxypheny) piperazine 2.8g and triethylamine 1.6g in dichloromethane 10ml under ** under ice-cooling, and was agitated at the room temperature for 1 hour. Water was added to the obtained reaction mixture and ethyl acetate extracted this, and after saturation brine washed the organic layer, it dried with magnesium sulfate. After it distilled off the solvent and the silica gel column chromatography which makes an eluate an n-hexane - ethyl-acetate mixed solvent (it is 2:1 at a capacity factor) refined the obtained residue, it recrystallized [mixed solvent / ethyl-acetate / the aforementioned n-hexane -], and 5-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran 3.5g (86% of yield) was obtained.
[0070] Melting point: 121-124-degree-CNMR delta (CDCl3) : 3.08 (4H, brs), 3.69 (2H, brs), 3.87 (3H, s), 4.00 (2H, brs) 6.81(1H,d),6.81-6.92(3H,m),6.92-6.94(1H,m),7.37(1H,d),7.42(1H,d),7.72(1H,d)
[0071]
[Example 2] 1-phenyl piperazine 540mg was used for the manufacture 5-benzofuran carboxylic acid of 5-(4-phenyl piperazinyl carbonyl) benzofuran (compound 2) and a hydrochloride instead of 600mg and 1-(2-methoxypheny) piperazine 2.8g, and 5-(4-phenyl piperazinyl carbonyl) benzofuran 610mg (64% of yield) was manufactured by the same method as (4) of an example 1.
[0072] Next, this 5-(4-phenyl piperazinyl carbonyl) benzofuran 610mg was dissolved in ethyl acetate, it considered as the solution, the solid-state which added the hydrogen chloride content ethyl-acetate solution to this solution 7%, and deposited was separated, and 5-(4-phenyl piperazinyl carbonyl) benzofuran and 690mg of hydrochlorides were obtained.
[0073] Melting point: 170-172-degree-CNMR delta (DMSO-d6) : 3.35 (4H, brs), 3.72 (4H, brs), 7.03 (2H, m), 7.33-7.44 (5H,

m)
7.68(1H,d),7.99(1H,d),8.09(1H,d)
[0074]
[Example 3] 1-(3-chlorophenyl) piperazine 650mg was used for the manufacture 5-benzofuran carboxylic acid of 5-[4-(3-chlorophenyl) piperazinyl carbonyl] benzofuran (compound 3) and a hydrochloride instead of 600mg and 1-(2-methoxypheny) piperazine 2.8g, and 5-[4-(3-chlorophenyl) piperazinyl carbonyl] benzofuran 460mg (41% of yield) was manufactured by the same method as (4) of an example 1.
[0075] Next, this 5-[4-(3-chlorophenyl) piperazinyl carbonyl] benzofuran 460mg was dissolved in ethyl acetate, it considered as the solution, the solid-state which added the hydrogen chloride content ethyl-acetate solution to this solution 7%, and deposited was separated, and 5-[4-(3-chlorophenyl) piperazinyl carbonyl] benzofuran and 510mg of hydrochlorides were obtained.
[0076] Melting point: 168-170-degree-CNMR delta (DMSO-d6) : 3.24 (4H, brs), 3.60 (4H, brs), 6.84 (1H, d), 6.94-7.02 (3H, m)
7.19(1H,t),7.38(1H,dd),7.67(1H,d),7.76(1H,d),8.09(1H,d)
[0077]
[Example 4] 1-(4-methoxypheny) piperazine 1.20g was used for the manufacture 5-benzofuran carboxylic acid of 5-[4-(4-methoxypheny) piperazinyl carbonyl] benzofuran (compound 4) instead of 0.95g and 1-(2-methoxypheny) piperazine 2.8g, and 5-[4-(4-methoxypheny) piperazinyl carbonyl] benzofuran 1.30g (73% of yield) was manufactured by the same method as (4) of an example 1.
[0078] Melting point: 125-126-degree-CNMR delta (CDCl3) : 3.09 (4H, brs), 3.77 (3H, s), 3.84 (4H, brs), 6.81-6.94 (5H, m)
7.40(1H,dd),7.55(1H,d),7.71(1H,dd)
[0079]
[Example 5] 1-(2-chlorophenyl) piperazine 3.0g was used for the manufacture 5-benzofuran carboxylic acid of 5-[4-(2-chlorophenyl) piperazinyl carbonyl] benzofuran (compound 5) instead of 2.5g and 1-(2-methoxypheny) piperazine 2.8g, and 5-[4-(2-chlorophenyl) piperazinyl carbonyl] benzofuran 500mg (36% of yield) was manufactured by the same method as (4) of an example 1.
[0080] Melting point: 175-176-degree-CNMR delta (CDCl3) : 3.06 (4H, brs),
3.71(2H,brs),3.96(2H;brs),6.82(1H,d),6.82-7.01(2H,m),7.01-7.21(2H,m),7.24-7.27(2H,m),7.36-7.42(2H,m),7.56(1H,dd),7.69(

[0081]
[Example 6] Manufacture of 7-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran (compound 6). [0082] (1) 2-BUROMO phenol 25.0g and BUROMO diethyl acetal 28.6g were used instead of manufacture 5-BUROMO phenol 35.0g of 7-bromobenzo furan, and 7-bromobenzo furan 16.1g (58% of yield) was obtained as oily matter by the same method as (1) of an example 1.
[0083] NMR delta (CDCl3):6.83 (1H, d), 7.11 (1H, dd), 7.46 (1H, d), 7.53 (1H, d), 7.68 (1H, d)
[0084] (2) 7-cyano benzofuran 9.8g (90% of yield) was manufactured by the same method as (2) of an example 1 using 7-bromobenzo furan 15.0g obtained above (1) instead of and 8.0g of copper cyanides. [manufacture 5-bromobenzo furan 18.0g of 7-cyano benzofuran]
[0085] Melting point: 57-58-degree-CNMR delta (CDCl3) : 6.88 (1H, d), 7.32 (1H, dd), 7.61 (1H, dd), 7.76 (1H, d), 7.85 (1H, dd)
[0086] (3) 10.3g (92% of yield) of 7-benzofuran carboxylic acids was manufactured by the same method as (3) of an example 1 using 7-cyano benzofuran 9.8g obtained above (2) instead of manufacture 5-cyano benzofuran 13.0g of 7-benzofuran carboxylic acid.
[0087] Melting point: 160-161-degree-CNMR delta (DMSO-d6):7.08 (1H, d), 7.38 (1H, dd), 7.88 (1H, d), 7.94 (1H, d), 8.13 (1H, d), 13.20 (1H, brs)
[0088] (4) 7-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran 730mg (70% of yield) of the purpose was manufactured by the same method as (4) of an example 1 using 500mg of 7-benzofuran carboxylic acids obtained above (3) instead of 2.0g of manufacture 5-benzofuran carboxylic acids of 7-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran.
[0089] Melting point: 91-92-degree-CNMR delta (CDCl3):3.04 (2H, brs), 3.21 (2H, brs), 3.55 (2H, brs), 3.87 (3H, s), 4.09 (2H, brs) and 6.82 (1H, d), 6.88-7.05 (4H, m), 7.30 (1H, dd) and 7.41 (1H, d), 7.66-7.68 (2H, m)
[0090]
[Example 7] manufacture 3-BUROMO-5-chloro-2-hydroxy benzaldehyde 25.0g, diethyl BUROMO malonate 50.7g, and 44.0g of potassium carbonate of a manufacture (1)5-chloro-7-bromobenzo furan-2-carboxylic acid of a 5-chloro-7-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran (compound 7) -- methyl-ethyl-ketone 110ml -- heating reflux was carried out in inside for 5 hours The depositing salt was ****(ed) after cooling, reduced pressure distilling off of the filtrate was carried out, and the 54g residue was obtained. 300ml of sulfuric-acid water and 300ml of ethyl acetate extracted this one by one 10%, and 150ml of ethyl acetate extracted the water layer twice further. The ethyl-acetate layer was dried with sulfuric-anhydride magnesium after washing by 375ml of saturation brine. Reduced pressure distilling off after **** and of the solvent was carried out for magnesium sulfate, and the 80g residue was obtained. 250ml of 10% potassium-hydroxide solution of ethanol nature was added to this, and after carrying out heating reflux for 1 hour, reduced pressure distilling off of the ethanol was carried out. Furthermore, 3l. water was added to this, and after carrying out the heating dissolution, the crystal which added the concentrated hydrochloric acid at the time of heat, and deposited was

separated. This crystal was separated after washing by 625ml of water, it dried, and 24.2g (83% of yield) of 5-chloro-7-bromobenzo furan-2-carboxylic acids was obtained.
[0091] Melting point: 204-205-degree-CNMR delta (DMSO-d6) : 7.69 (1H, s) 7.87 (2H, s)
[0092] (2) 5-chloro-7-cyano benzofuran 6.6g (57% of yield) was obtained for the 5-chloro-7-bromobenzo furan-2-carboxylic acid obtained above (1) instead of manufacture 5-bromobenzo furan 18.0g of a 5-chloro-7-cyano benzofuran by the same method as (2) of an example 1 using 18.0g and 8.2g of copper cyanides.
[0093] Melting point: 133-134-degree-CNMR delta (CDCl3) : 6.84 (1H, d), 7.58 (1H, d), 7.80 (1H, d), 7.82 (1H, d)
[0094] (3) 5.8g (90% of yield) of 5-chloro-7-benzofuran carboxylic acids was manufactured by the same method as (3) of an example 1 using 5-chloro-7-cyano benzofuran 5.8g obtained above (2) instead of manufacture 5-cyano benzofuran 13.0g of a 5-chloro-7-benzofuran carboxylic acid.
[0095] Melting point: 215-216-degree-CNMR delta (DMSO-d6):7.04 (1H, d), 7.76 (1H, d), 8.01 (1H, d), 8.18 (1H, d), 13.51 (1H, brs)
[0096] (4) 5-chloro-7-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran 670mg (71% of yield) of the purpose was manufactured by the same method as (4) of an example 1 using 500mg of 5-chloro-7-benzofuran carboxylic acids obtained above (3) instead of 2.0g of manufacture 5-benzofuran carboxylic acids of a 5-chloro-7-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran.
[0097] Melting point: 139-141-degree-CNMR delta (CDCl3):3.03 (2H, brt), 3.19 (2H, brt), 3.54 (2H, brt), 3.87 (3H, s), 4.06 (2H, brt) and 6.78 (1H, d), 6.87-7.08 (4H, m), 7.38 (1H, d), 7.63 (1H, d), 7.69 (1H, d)
[0098]
[Example 8] Manufacture of a 2-(N'-acetyl hydrazono) methyl-5-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran (compound 8). [0099] (1) manufacture 5-BUROMO-2-hydroxy benzaldehyde 25.0g of a 5-BUROMO-2-ethoxycarbonyl benzofuran, diethyl BUROMO malonate 50.0g, and 51.4g of potassium carbonate -- methyl-ethyl-ketone 100ml -- heating reflux was carried out in inside for 5 hours The depositing salt was ****(ed) after cooling, reduced pressure distilling off of the filtrate was carried out, 300ml of sulfuric-acid water and 300ml of ethyl acetate extracted the obtained residue one by one 10%, and 150ml of ethyl acetate extracted the water layer twice further. The ethyl-acetate layer was dried with sulfuric-anhydride magnesium after washing by 375ml of saturation brine. The silica gel column chromatography which makes an eluate an n-hexane - ethyl-acetate mixed solvent (it is 20:1 at a capacity factor) separated the residue obtained solvent / after **** and] by carrying out reduced pressure distilling off in magnesium sulfate, and 5-BUROMO-2-ethoxycarbonyl benzofuran 28.2g (90% of yield) was obtained.
[0100] Melting point: 59-60-degree-CNMR delta (CDCl3) : 1.42 (3H, t) 4.44 (2H, q)
7.45(1H,s),7.46(1H,d)
7.53(1H,dd),7.81(1H,d)
[0101] (2) 5-cyano-2-ethoxycarbonyl benzofuran 11.1g (47% of yield) was obtained for the 5-bromobenzo furan-2-ethoxycarbonyl benzofuran obtained above (1) instead of manufacture 5-bromobenzo furan 18.0g of a 5-cyano-2-ethoxycarbonyl benzofuran as oily matter by the same method as (2) of an example 1 using 13.0g and 5.1g of copper cyanides.
[0102] NMR delta (CDCl3) : 1.44 (3H, t), 4.47 (2H, q), 7.57 (1H, s), 7.71 (2H, m), 8.07 (1H, d)
[0103] (3) 50ml [of water] and ethanol 50ml was added to 5-cyano-2-ethoxycarbonyl benzofuran 11.1g and 2.1g of sodium hydroxides obtained with the manufacture above (2) of a 5-cyano-2-hydroxymethyl benzofuran, and heating reflux was carried out for 1 hour. After cooling reaction mixture to a room temperature, ethanol was distilled off and the residue was dissolved in water. After adding a concentrated hydrochloric acid to this solution, it extracted by the tetrahydrofuran. After saturation brine washed this tetrahydrofuran solution, it dried with magnesium sulfate, reduced pressure distilling off of the solvent was carried out, and the 10.0g residue was obtained. After adding triethylamine 12.3ml and tetrahydrofuran 200ml to the residue and carrying out the bottom chloro ethyl carbonate of ice-cooling under **, it agitated at the room temperature for 30 minutes. The triethylamine hydrochloride which deposited was ****(ed), and filtrate (tetrahydrofuran solution) was used as boron-hydride sodium 6.1g 200ml solution of water under bottom ** of ice-cooling, and was agitated at the room temperature for 3 hours. 300ml of bottom 1-N hydrochloric acids of ice-cooling was made under ** the obtained reaction mixture, ethyl acetate extracted the water layer, and the organic layer was dried with sulfuric-anhydride magnesium after washing with saturation brine. The solvent was distilled off, the silica gel column chromatography which makes an eluate an n-hexane - ethyl-acetate mixed solvent (it is 1:1 at a capacity factor) refined the obtained residue, and 5-cyano-2-hydroxymethyl benzofuran 5.8g (62% of yield) was obtained.
[0104] Melting point: 105-108-degree-CNMR delta (CDCl3):2.06 (1H, brs), 4.82 (2H, s), 6.74 (1H, s), 7.55 (1H, s), 7.90 (1H, s)
[0105] (4) 20.0g of chromic acids was added to the manufacture pyridine 32ml [of a 2-(1, 3-dioxolane-2-IRU)-5-benzofuran carboxylic acid] dichloromethane 400ml solution, 5-cyano-2-hydroxymethyl benzofuran 5.8g obtained above (3) after 15 minutes was added, and it agitated for 15 minutes at the room temperature. After decanting and taking the supernatant liquid, washing the residue by the dichloromethane and a supernatant liquid, 1-N sodium-hydroxide solution in all, 1-N hydrochloric acid, saturation sodium-hydrogencarbonate solution, and saturation brine washing this solution one by one, it dried with magnesium sulfate. Heating reflux was carried out for 2 hours, having distilled off the solvent, having added toluene 100ml, ethylene glycol 3.10g, and 100mg of p-toluenesulfonic acid to the obtained residue, and removing water by the Dean Stark trap. The obtained reaction mixture was washed in saturation carbonic acid hydrogen NATORIU solution, and it dried with magnesium sulfate. The solvent was distilled off, ethylene glycol 60ml, 60ml of water, and 6.60g of potassium hydroxides

were added to the obtained residue, and heating reflux was carried out for 1 hour. The obtained reaction mixture was made acid with the bottom 1-N hydrochloric acid of ice-cooling, and ethyl acetate extracted. The organic layer was dried with magnesium sulfate after washing with saturation brine, the solvent was distilled off, it recrystallized in the n-hexane - ethyl-acetate mixed solvent, and 4.30g (55% of yield) of 2-(1, 3-dioxolane-2-IRU)-5-benzofuran carboxylic acids was obtained.
[0106] Melting point: 300-degree-Cor more NMR delta (CDCl3):4.10-4.21 (4H, m), 6.11 (1H, s), 6.91 (1H, s), 7.54 (1H, d)
[0107] (5) After adding KARUBOJI imidazole 410mg to 2-(1, 3-dioxolane-2-IRU)-5-benzofuran carvone 590mg obtained with the manufacture above (4) of a 2-(1, 3-dioxolane-2-IRU)-5-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran and agitating at a room temperature for 1 hour, 1-(2-methoxypheny) piperazine 490mg was added, and it agitated at the room temperature for further 1 hour. Ethyl acetate was added to the obtained reaction mixture, and it washed in saturation sodium-hydrogencarbonate solution, and dried with sulfuric-anhydride magnesium. The solvent was distilled off, the silica gel column chromatography which makes an eluate an n-hexane - ethyl-acetate mixed solvent (it is 1:1 at a capacity factor) refined the obtained residue, and 2-(1, 3-dioxolane-2-IRU)-5-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran 430mg (43% of yield) was obtained as oily matter.
[0108] NMR delta(CDCl3): -- 3.02 (4H, brs) and 3.63 (2H, brs)
3.88(3H,s),3.98(2H,brs),4.09-4.20(4H,M),6.10(1H,s),6.85-6.94(3H,M),7.02-7.10(1H,m),7.40(1H,d),7.53(1H,d),7.69(1H,S
[0109] (6) 2-(1, 3-dioxolane-2-IRU)- obtained with the manufacture above (5) of a 2-(N'-acetyl hydrazono) methyl-5-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran -- the solvent after adding ethanol 20ml and 10ml of 1-N hydrochloric acids to 5-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran 430mg and heating at 50 degrees C for 1 hour -- distilling off . Saturation sodium-hydrogencarbonate solution was added gradually. After ethyl acetate extracted the water layer, saturation brine washed the organic layer and it dried with sulfuric-anhydride magnesium. the residue obtained by carrying out reduced pressure distilling off of the solvent -- acetyl hydrazine 90mg -- adding -- ethanol 5ml -- time heating reflux was carried out in inside Reduced pressure distilling off of the solvent of reaction mixture was carried out, the silica gel column chromatography which makes an eluate a dichloromethane - methanol mixed solvent (it is 20:1 at a capacity factor) refined the obtained residue, and 2-(N'-acetyl hydrazono) methyl-5-[4-(2-methoxypheny) piperazinyl carbonyl] benzofuran 300mg (60% of yield) of the purpose was obtained.
[0110] Melting point: 194-195-degree-CNMR delta (CDCl3):1.65 (3H, s),
2.44(3H,s),3.10(4H,brs),3.65(2H,brs),4.02(2H,brs),6.88-7.02(5H,m),7.48(1H,d),7.54(1H,d),7.72(1H,s),7.82(1H,s),10.01(1H,b

[0111]
[Example 9] Heating reflux was carried out for 12 hours, after making it under ** the dichloromethane 200ml suspension of 53.0g of aluminum chlorides under ice-cooling of a dichloromethane 100ml solution (manufacture 2-ethoxycarbonyl benzofuran 10.0g of the manufacture (1)5-acetyl-2-ethoxycarbonyl benzofuran of 5-[3-{4-(2-methoxypheny) piperazinyl} propionyl] benzofuran (compound 9), and acetyl chloride 41.0g) and agitating at a room temperature for 1 hour. The obtained reaction mixture was gradually added to iced water. Ethyl acetate extracted this reaction processing liquid, and it dried with sulfuric-anhydride magnesium after washing with saturation brine. Reduced pressure distilling off of the solvent was carried out, the silica gel column chromatography which makes an eluate an n-hexane - ethyl-acetate mixed solvent (it is 10:1 at a capacity factor) refined the obtained residue, and 5-acetyl-2-ethoxycarbonyl benzofuran 11.0g was obtained as oily matter.
[0112] NMR delta (CDCl3):1.45 (3H, t), 2.68 (3H, s), 4.47 (2H, q), 7.60 (1H, s), 7.64 (1H, s), 8.09 (1H, d), 8.33 (1H, d)
[0113] (2) Ethanol 15ml and 15ml of water were added to 5-acetyl-2-ethoxycarbonyl benzofuran 3.15g and 1.14g of sodium hydroxides obtained with the manufacture above (1) of 5-acetyl benzofuran, and heating reflux was carried out for 1 hour. The obtained reaction mixture was made acid with 1-N hydrochloric acid, and the crystal which deposited was separated and rinsed. 100mg [of copper powder] and quinoline 10ml was added to this crystal, and heating reflux was carried out for 1 hour. Ethyl acetate was added after cooling the obtained reaction mixture, and subsequently saturation brine washed the organic layer once 3 times with 6-N hydrochloric acid, and it dried with sulfuric-anhydride magnesium. Reduced pressure distilling off of the solvent was carried out, the silica gel column chromatography which makes an eluate an n-hexane - ethyl-acetate mixed solvent (it is 10:1 at a capacity factor) refined the obtained residue, and the 5-acetyl benzofuran 850mg crystal was obtained.
[0114] Melting point: 39-41-degree-CNMR delta (CDCl3):2.66 (3H, s), 6.86 (1H, s), 7.54 (1H, d), 7.69 (1H, s), 7.95 (1H, d), 8.26 (1H, s)
[0115] (3) 1.5ml of concentrated hydrochloric acids was added to the manufacture 1-(2-methoxypheny) piperazine 1.70g [of 5-[3-{4-(2-methoxypheny) piperazinyl} propionyl] benzofuran] ethanol 10ml solution, and reduced pressure distilling off of the solvent was carried out after 1-hour churning at the room temperature. The 5-acetyl benzofuran 1.08g 95% ethanol 10ml solution obtained by the obtained residue with paraformaldehyde 600mg, 0.02ml of concentrated hydrochloric acids, and the above (2) was added, and heating reflux was carried out for 10 hours. After cooling the obtained reaction mixture, the solvent was distilled off, the residue was diluted with 1-N sodium hydroxide, and ethyl acetate extracted. After saturation brine washed the organic layer, it dried with sulfuric-anhydride magnesium. After carrying out reduced pressure distilling off of the solvent, the silica gel column chromatography which makes an eluate an n-hexane - ethyl-acetate mixed solvent (it is 2:1 at a capacity factor) refined the obtained residue, and 1.45g (69% of yield) of crystals of the target 5-[3-{4-(2-methoxypheny) piperazinyl} propionyl] benzofuran was obtained.
[0116] Melting point: 132-133-degree-CNMR delta (CDCl3):2.77 (4H, brs), 2.96 (2H, t), 3.13 (4H, brs), 3.31 (2H, t), 3.87 (3H, s), 6.85-6.92 (2H, m), 6.94-7.03 (3H, m), 7.56 (1H, d), 7.70 (1H, d), 7.98 (1H, dd), and 8.29 (1H, d) -- on the other hand,